Current Good Manufacturing Practices and Current Good Compounding Practices

cGMP and cGCP

GMP

GMP regulations established by FDA to

- **Ensure that minimum standards present for drug product quality.**

- The cGMP regulations for:

bulk and **finished pharmaceutical products**).

c GMP REGULATIONS include

1. **Organization and Personnel**
2. **Personnel qualifications and Personnel responsibilities.**
3. **Buildings:** Design and Lighting, Ventilation, air filtration, air heating and cooling, Sanitation , Maintenance
4. **Equipment:** design, size, and location, Equipment construction, cleaning and maintenance.

1. **Filters**
2. **Containers and Closures**
3. Test drug: **approval or rejection of components**, **drug product containers, and closures**
4. Use of approved components, drug product containers, and closures
5. **Retesting of approved components**, drug product containers, and closures
6. **Rejected** components, drug product containers, and closures

F. **Production and Process Controls**: **Written procedures should present**.

1. Calculation of yield
2. Equipment identification
3. **Sampling and testing of in-process materials and drug products**

- **Active pharmaceutical ingredient (API):** Any component have pharmacologic activity in diagnosis, cure, mitigation, treatment or prevention of disease.
- **Batch:** **A specific quantity of a drug** of uniform specified quality produced according to single manufacturing order during the same cycle of manufacture.
- **Certification:** Documented testimony by qualified authorities that a system qualification, calibration, validation, or revalidation has been performed.
- **Compliance:** manufacturer acting with prescribed regulations, standards, and practices.

- **Component:** Any ingredient used in manufacture of drug product.
- **Drug product:** Finished form contains active drug and inactive ingredients.
- **Inactive ingredient:** Any component other than the active ingredients in drug product.
- **Lot:** A batch or any portion of a batch having uniform specified quality and a distinctive identifying lot number.
- **Lot number, control number, or batch number:** combination of letters, numbers, or symbols from which the complete history of manufacture, processing, packaging, holding, and distribution of a batch or lot of a drug product may be determined.

- **Master record:** **Record containing the formulation**, specifications, manufacturing procedures, quality assurance requirements, and labeling of finished product.
- **Quality assurance:** all evidence needed that activities relating to quality are being performed adequately.
- **Quality control:** process through which industry measures actual quality performance, compares it with standards.

- **Quality control unit:** organizational element designated by a firm to be responsible for work related to quality control.

- **Quarantine:** An area that is marked, designated, or set aside for the holding **of incoming components** **prior to acceptance testing** and qualification for use.

- **Representative sample:** A sample that represent the whole product.
- **Reprocessing:** **recycling:** The activity that finished product or any of its components is recycled through all or part of the manufacturing process.
- **Strength:** concentration of drug per unit dose or volume.
- **Verified:** Signed by a second individual or recorded by automated equipment.
- **Validation:** Documented evidence that a system (e.g., equipment, software, controls) does what it purports to do.
- Process validation: Documented evidence that a process (e.g., sterilization) does what it purports to do.
- Validation protocol: experimental plan to produce documented evidence that the system has been validated.

Organization and personnel

- deals with responsibilities of quality control unit, employees, and consultants.
- quality control unit have responsibility for all functions that affect product quality. This includes **accepting** or **rejecting** product components, product specifications, finished products, packaging, and labeling. Adequate laboratory facilities shall be provided, written procedures followed, and all records maintained.
- All personnel required to have **education, training, and experience**
- Appropriate programs of education and training, and performance evaluations are essential for maintaining quality assurance.

EQUIPMENT

- Each piece of equipment must be :**appropriate design** and **size** to facilitate **use, cleaning, and maintenance**.
- equipment's surfaces and parts **must not interact** with processes or product s so not affect **purity, strength**, or **quality.**
- Standard operating **procedures must be written** and followed for proper use, maintenance, and cleaning of each piece of equipment.
- equipment and computers used in the processes must be **routinely calibrated**, maintained, and validated for accuracy.
- Filters used in the manufacture or processing of injectable drug products **must not** release fibers into such products.

Control of componants, containers and closure

- Written procedures, identification, storage, handling, sampling, testing, and **approval or rejection** of all product components, containers, and closures must be maintained and followed.
- Bulk pharmaceutical chemicals, containers, and closures must meet the required property.
- Raw materials should verified through sampling and qualitative and quantitative analysis.
- **Rejected components**, containers, and closures are identified and controlled under a **quarantine system** to prevent their use in manufacturing and processing operations.

- Mainly bulk chemicals (APIs) are synthesized in **China and India**
- it is important to confirm their identity and purity with **USP** and **NF** prior to use in finished pharmaceuticals.

PRODUCTION AND PROCESS CONTROLS

- **Written procedures** are required to ensure that drug products have correct **identity**, **strength**, **quality**, and **purity**.

- In-process samples taken from production batches periodically for product control.

Packaging and labeling control

- Written procedures are required for the receipt, identification, storage, handling, sampling, and testing of drug product and issuance of labeling and packaging materials.
- **Expiration Dating**

Expiration Dating

- To ensure that a drug product meets standards of identity, strength, quality, and purity at time of use.

- Except from this requirement are **homeopathic drug products**, **allergenic extracts**, and investigational drugs that meet the standards established during preclinical and clinical studies.

HOLDING AND DISTRIBUTION

- Written procedures must be established and followed for the holding and distribution of product.
- Finished pharmaceuticals must be quarantined in storage until released by the quality control unit.
- Products must be stored and **shipped** under conditions that **do not affect product quality.**
- the oldest approved stock is distributed first.
- The distribution control system must allow the distribution point of each lot of drug product to be readily determined to facilitate its recall if necessary.

LABORATORY CONTROLS

- Laboratory controls are requirements for the establishment of and conformance to :
- **written specifications**,
- **standards**,
- **sampling plans**,
- **test procedures**.
- The specifications, which apply to each batch of drug product, include **sample size**
- **test intervals**
- **sample storage**
- **stability testing**

special testing requirements for parenterals, ophthalmics , controlled-release products, and radioactive pharmaceuticals.

Complete master production and control records for each batch must be kept and include the following:

- Name and strength of the product
- Dosage form
- Quantitative amounts of components.
- Complete manufacturing and control procedures
- Equipment used
- In-process controls
- Sampling and laboratory methods and assay results
- Calibration of instruments
- Distribution records
- Dated and employee-identified records

ADDITIONAL cGMP REQUIREMENTS

Active Pharmaceutical Ingredients and Excipients

The quality of any finished product depends on the quality of the components, and active ingredients.

GMP focuses on all elements of chemical purity and quality, including following:

- **Specifications and analytical methods for all reactive and nonreactive components** used.
- chemical reaction steps
- Handling of chemical intermediates
- Quality of water used.
- Solvent handling and recovery systems
- Analytical methods to detect impurities or chemical residues and limits set
- Stability studies of bulk pharmaceutical chemical

MEDICAL DEVICES

1. devices are approved for marketing when shown to be safe and effective through premarket approval.
2. Medical devices are subject to the reporting of adverse events, to recall, and to termination of approval.
3. The regulations for "good manufacturing practice for medical devices" are similar to those for finished pharmaceuticals. They include **personnel**; **buildings**; **equipment**; **control of components**; production and process controls; packaging and labeling; holding, distribution, and installation; device evaluation; and records.

- Devices covered by cGMP regulations include:

1. **intraocular lenses,**
2. **hearing aids,**
3. **intrauterine devices,**
4. **cardiac pacemakers,**
5. **clinical chemistry analyzers,**
6. **catheters,**
7. **cardiopulmonary bypass heart-lung machine console,**
8. **dental X-ray equipment,**
9. **surgical gloves,**
10. **prosthetic hip joints,**
11. **traction equipment,**
12. **computed tomography equipment, and**
13. **powered wheelchairs.**

USP-NF FORMULARY

- In the **absence of stability information**, the following maximum time use after opening are recommended for **non sterile** compounded drug preparations that are packaged in tight, light-resistant containers and stored at controlled room temperature:

1. For **non aqueous liquids and solid** formulations:

(a) Where manufactured drug product is the source of active ingredient, the beyond-use date is **not later than 25%** of the time remaining until the product's expiration date or 6 months.

(b) where a USP or NF substance is the source of active ingredient, the beyond-use date is not later than 6 months.

- For water-containing formulations prepared from ingredients in solid form, the beyond-use date is not later than **14 days** when stored at cold temperatures.

- For all other formulations, use date is not later than intended duration of therapy or **30 days**.
- **If no sterility testing program is in place, the following apply:**

1. For low-risk preparations at room temperature use dates not more than **48 hours** and for refrigerated temperatures, not more than **14 days**.
2. For medium-risk preparations at room temperature, use **not more than 30 hours** and for **refrigerated temperatures, not more than 9 days.**
3. For high-risk preparations at room temperature, **not more than 24 hours** and for **refrigerated temperatures, not more than 3 days.**

In all three instances, if stored at -25°C to -10°C, the beyond-use dates are 45 days in the solid state.

CONTAINERS

- must **provide adequate drug stability**.

qualities tested for containers

1. Physicochemical properties.
2. Light-transmission for glass or plastic.
3. Drug compatibility.
4. Leaching and/or migration.
5. Vapor transmission for plastics.
6. Moisture barrier.
7. Toxicity for plastics.
8. Valve, actuator, metered dose, particle size, spray characteristics, and leaks for aerosols.
9. Sterility and permeation for parenteral containers.
10. Drug stability for all packaging.

- According to USP, a **container is** “that which **holds the article** and is **or in direct contact with article**.” The immediate container is “that which is in direct contact with the article at all times.”
- The closure is part of the container.

- The container, should be **clean and dry** before it is filled with drug.
- must not interact physically or chemically with the drug.

- Ex: sorption of diazepam, to low density plastics resulting in a loss of drug avoided with the use of glass containers.

The USP classifies containers according to their ability to protect their contents from external conditions.

1. **well-closed container**. "protects contents from solids and from loss under ordinary conditions of handling, shipment, storage, and distribution."
2. **A tight container** "protects contents from contamination by liquids, solids, or vapors, or evaporation under the ordinary conditions of handling, shipment, storage, and distribution and is capable of tight re-closure."

3. **A hermetic container** “is impervious to air or any other gas under the ordinary conditions of handling, shipment, storage, and distribution.”

4. **Sterile hermetic containers** hold preparations intended for injection or parenteral administration.

- **A single-dose container :**when opened, cannot be resealed with assurance that sterility has been maintained.
- These containers include **fusion sealed ampoules** and **prefilled syringes and cartridges**.

- **A multiple-dose container** is a **hermetic container** that permits withdrawal of successive portions of the contents without changing the strength or affect the quality or purity of the remaining portion. These containers are commonly called **vials**.

- **unit dose package:** positive identification of each dosage unit and **reduction of errors**, **reduced contamination** of the drug.
- packaging materials may be combinations of paper, foil, plastic, or cellophane.

Oral liquids

- dispensed in single units in paper, plastic, or foil cups or prepackaged and dispensed in glass containers having threaded caps or crimped aluminum caps.
- disposable plastic oral syringes with rubber or plastic tips on the orifice for closure.

- suppositories, powders, ointments, creams, and ophthalmic solutions, are also commonly found in single-unit packages.

unit-of-use packaging

- the quantity of drug product prescribed is packaged in a container.

- Ex: if certain antibiotic capsules are prescribed to be taken 4 times a day for 10 days, unit-of-use packaging would contain 40 capsules. Other products may be packaged to contain a month's supply.

light-resistant containers

- **Amber glass** or a light-resistant **opaque plastic** will reduce light transmission sufficiently to protect a **light-sensitive** pharmaceutical.
- **ultraviolet absorbers** may be added to plastic to decrease the transmission of short ultraviolet rays.
- USP standards that define the acceptable limits of light transmission at any wavelength between 290 and 450 nm.

- recent innovation in plastic packaging is the **coextruded two-layer high-density polyethylene bottle**, which has an **inner layer** of **black polyethylene coextruded** with an **outer** layer of **white polyethylene**. The container provides:

1. **light resistance.**
2. **moisture protection**.

Increasingly being used in packaging of tablets and capsules.

Glass used in packaging pharmaceuticals

- 4 categories :
- **Types I, II, and III** intended for **parenteral products**, and type**IV: NP** is intended for other products.
- Each type tested according to resistance to water attack.
- Degree of attack is determined by **amount of alkali released** from glass in specified test conditions.
- leaching of alkali from glass to preparation could alter

1. pH
2. Stability of product.

- Type I is most resistant glass of 4 categories.

- **Today**, most products are packaged in **plastic**.
- intravenous fluids, plastic ointment tubes, plastic film-protected suppositories, and plastic tablet and capsule vial.

- **Advantage over glass:**

1. **Light** and resistance to impact, which reduces costs and losses due to container damage
2. Versatility in container design, consumer acceptance
3. Consumer preference for plastic squeeze bottles in administration of ophthalmics, nasal sprays, and lotions
4. The popularity of blister packaging and unit-dose dispensing.

- **Example**, Addition of **methyl groups** to every other carbon atom in the polymer chains of **polyethylene** will give **polypropylene**, material that can be **autoclaved**.
- If a **chlorine** atom is added to every other carbon in the **polyethylene** polymer, **polyvinyl chloride** (PVC) is produced. This material is **rigid and has good clarity**, making it particularly useful in the **blister packaging** of tablets and capsules. However, it has a significant drawback for packaging medical devices (e.g., syringes): it is **unsuitable for gamma sterilization**, a method that is being used increasingly.

- The placement of other functional groups on the main chain of **polyethylene** or added to polymers can give a variety of alterations to final plastic material. Among the newer plastics are **polyethylene terephthalate** (PET), **amorphous polyethylene terephthalate** glycol (APET), and polyethylene terephthalate glycol (PETG). Both APET and PETG have excellent **transparency** and can be **sterilized with gamma radiation**.

- Among **problems** encountered in the use of **plastics** in packaging are:
- (a) **Permeability of containers to atmospheric oxygen and moisture vapor.**
- (b) **Leaching of constituents of to the internal contents.**
- (c) **Absorption of drugs from contents to container.**
- (d) **transmission of light through container**.
- (e) **Alteration of container upon storage**.
- **plasticizers, stabilizers, antioxidants, antistatic agents, antifungal agents, colorants, and others.**

- The permeability of a plastic is a function of:

1. Nature of polymer;
2. the amounts and types of plasticizers,
3. fillers, lubricants, pigments and other additives;
4. pressure; and temperature.

- Increases in temperature, pressure, and the use of additives tend to increase permeability of plastic. Glass containers are less permeable than plastic containers.

- Many products liable to deteriorate in humidity unless protected by high-barrier packaging.
- Desiccant silica gel in small packets, commonly included as protection against effects of moisture vapor.
- Drug substances that are subject to **oxidative degradation** may undergo a greater degree of degradation when packaged in plastic than in glass.
- Liquid in plastic may **lose drug molecules** or solvent to the container, altering the concentration of drug in product and affecting its potency.

- **Leaching** is term used to describe **movement of components of container to contents**.
- Compounds leached: polymer additives, such as the plasticizers, stabilizers, or antioxidants. **The leaching occurs when liquids or semisolids are packaged in plastic.** Little leaching occurs when tablets or capsules are packaged in plastic.
- influenced by temperature, agitation

- **Sorption** indicate **binding of molecules to polymer** includes both **adsorption and absorption**.
- Sorption occurs through chemical or physical means.
- **un-ionized species of solute has greater tendency to bound than ionized species.**
- degree of ionization of a solute affected by pH of solution, the pH may influence sorption of particular solute.
- **Plastic materials with polar groups are prone to sorption.** Because **sorption depends on penetration or diffusion of a solute into plastic.**

- **Sorption** may occur with **active pharmacologic agents** or **with excipients**.
- Sorption may be initiated by the **adsorption of a solute to the inner surface of a plastic container.**
- After saturation of the surface, the solute may diffuse into the container and bound within plastic.
- The sorption of excipients :colorants, preservatives, or stabilizers would likewise alter the quality of product.
- Methylparaben may be sorbed to some types of plastics, resulting in a decrease in the available concentration of preservative.

- Deformations, softening, hardening, and other physical changes in plastic containers can be caused by the action of container's contents or external factors, including changes in temperature and physical stress placed upon the container in handling and shipping.

Child-Resistant & Adult-Senior use Packaging

- Defined as one that is significantly difficult for children under 5 years of age to open or to obtain a harmful amount of its contents within a reasonable time and that is not difficult for “normal adults” to use properly.

Compliance packaging

- blister packaging in a calendar pack.
- These medication compliance useful for :**patients taking multiple medications.**

LABELING

- company literature
- advertising and promotional material
- booklets, mailing pieces, file cards, price lists, catalogs, sound recordings, film strips, motion picture films, slides, exhibits, displays, literature reprints, and computer-accessed information; and other materials related to the product.
- Important information for a prescription-only drug.

MANUFACTURER'S LABEL

- The nonproprietary name of drug or The name of the manufacturer, packer, or distributor of the product.
- A quantitative statement of the amount of each drug per unit of weight, volume, or dosage unit.
- The pharmaceutical type of dosage form constituting the product
- The net amount of drug product contained in the package, in units of weight, volume, or number of dosage units, as appropriate
- The logo "Rx only" or the federal legend "Caution—Federal law prohibits dispensing without prescription" or a similar statement.
- A label reference to refer to the accompanying package insert or other product literature for dosage and other information.
- Special storage instructions when applicable.
- The National Drug Code identification number for the product (and often a bar code)
- An identifying lot or control number.
- An expiration date.
- "Warning—May be habit forming" may also appear.

PRESCRIPTION LABEL

- **Name and address of the pharmacy**
- Serial number of prescription
- Date of the prescription or the date of its filling or refilling (state law often determines which date is to be used).
- Name of prescriber
- Name of patient
- Directions for use, include any precautions, as indicated on prescription.

1. The address of the patient
2. The initials or name of the dispensing pharmacist
3. The telephone number of the pharmacy
4. The drug name, strength, and manufacturer's lot or control number
5. The expiration date of the drug
6. The name of the manufacturer or distributor
7. In an effort to decrease medication errors, there is thought to include the “indication” on the prescription label to help the pharmacist assure the prescribed drug is appropriate.

OVER-THE-COUNTER LABELING

- Product name.
- Name and address of manufacturer, packer or distributor.
- Quantity of contents.
- Names and quantities of all active ingredients /dosage unit. Inactive ingredients also listed.
- Name of any habit-forming substance or substances in the preparation.
- Statement of pharmacologic category (e.g., antacid) and adequate directions for safe and effective use, for example, dose, frequency of dose, dose and age considerations, route of administration, and preparation for use, such as shaking or dilution.

- Cautions and warnings.
- Sodium content for certain oral products intended for ingestion, when the product contains 5 mg of sodium or more/single dose or 140 mg or more in maximum daily dose.
- Storage conditions.
- Lot number and expiration date.

- geriatric patients, might be unable to read a label physically, easy-to-read font size is required along with other graphical features that promote the ability to read the label information.

Dietary Supplement Labeling

- Should write: "**improve mood**" rather than treat depression
- Should write :**This product is not intended to diagnose, treat, cure, or prevent any disease**."
- For herbal products, the label must also state **the part of the plant used to make the product**, for example, root, stem, leaf.
- minimum information about the product prior to its use.

STORAGE

- product must be stored in proper conditions.
- The labeling of product includes **the desired conditions of storage.**
- **Cold:** Any temperature not exceeding **8°C.**
- A **refrigerator** is a cold place in which the temperature is maintained thermostatically between **2° and 8°C**.
- **A freezer** is a cold place in which the temperature is maintained thermostatically **between -25° and -10°C.**
- **Cool:** Any temperature between **8° and 15°C**.

- **Room temperature:** The temperature in a working area. 20° to 25°C.
- **Warm:** Any temperature between **30° and 40°**C.
- **Excessive heat**: **Above 40°**C.
- Protection from freezing: in addition to the **risk of breakage** of container, freezing subjects a product to **loss of strength** or **potency** or to **destructionof dosage form**.
- TRANSPORTATION
- The stability protection of a pharmaceutical product during transportation is important.

STORAGE

chapter 4

Dr. yasir saber

lecture 8

- **Stability**
- Drugs can be classified according to their sensitivity to breakdown:
- 1. **Stable under all conditions** (e.g. kaolin)
- 2. **Stable if handled correctly** (e.g. aspirin)
- 3. **Moderately stable even with special handling** (e.g. vitamins)
- 4. **Very unstable** (e.g. certain antibiotics in solution form).

- Initial investigation begins with the knowledge of the drug`s chemical structure.
- Chemically, the most frequently encountered decomposition processes are **hydrolysis** and **oxidation.**

- Stability studies should include:
  - **solid state stability**
  - **solution stability**
  - **stability in the presence of excipients**

Drug Stability: Mechanisms of Degradation

- **Chemically**, drug are alcohols, phenols, aldehydes, ketones, esters, ethers, acids, salts, alkaloids, glycosides, and others
- most destructive processes are **hydrolysis and oxidation.**
- Hydrolysis is a solvolysis (drug interact with water)to yield breakdown products.
- example, aspirin

Five types of stability concern pharmacists:

1. **Chemical**: processes:**hydrolysis** and **oxidation**.
2. **Physical:** appearance, palatability, uniformity, dissolution.
3. **Microbiologic:** Sterility or resistance to microbial growth.
4. **Therapeutic:** The therapeutic effect remains unchanged.
5. **Toxicologic:** No significant increase in toxicity occurs.

- **Chemical stability is important for selecting storage conditions (temperature, light, humidity), selecting the proper container for dispensing (glass or plastic, clear or amber or opaque).**

Enhancing Stability of Drug Products

1. **elimination of water** from pharmaceutical. applying **waterproof protective coat** over tablets or keep drug in **tightly closed container**.
2. In liquid preparations, **water replaced** in formulation with liquids such as **glycerin, propylene glycol, and alcohol**.

- In certain injectable products, anhydrous vegetable oils used as solvent to reduce hydrolytic decomposition.

- **Hydrolysis prevented** in liquid: **nonaqueous** vehicle.
- Antibiotic: drug **dry** for reconstitution with water before dispensing.

3. **Refrigeration** advisable for preparations subject to hydrolysis. Together with **temperature, pH** is major determinant of stability.

- Hydrolysis depends on **conc of hydroxyl** and hydronium ions, and pH .

4. For hydrolyzable drugs, **optimum stability** is on acid side, between **pH 5 and 6**. through use buffering agents.

- **Oxidation occur in oxygen** or **light**.
- Oxidation accompanied by alteration in **color** of formula. It may also result in **precipitation** or a change in **odor**.
- inhibited by **antioxidant**s.

- **Light** can also act as a **catalyst** to oxidation.
- sensitive preparations packaged in **light-resistant** or opaque containers.

- **Degradations** proceed rapidly as **temp increase,**
- Maintain in **cool** place.
- Stability in solution: **pH** of the preparation. Each drug must be maintained in solution at pH most favorable to stability.
- **Stabilize preparation by :**

1. **exclusion from oxygen**,
2. **oxidizing agents**,
3. **trace metals**,
4. **light**,
5. **heat**, and
6. other **chemical catalysts** to oxidation process.

Add

1. **Antioxidants**,
2. chelating agents.
3. buffering agents to create favorable pH.

Stability and expiration dating are based on reaction **kinetics**

Zero order

the loss of drug is independent of the concentration of the reactants and constant with respect to time (ex., I mg/hour).

$C = -k_0 t + C_0$

$t_{1/2} = 0.5 (C_0 / k_0)$

Example: A suspension (125 mg/ml) decays by zero-order kinetics with a reaction rate constant of 0.5 mg/ml/hour. What is the concentration of intact drug remaining after 3 days (72 hours) and what is its $t_{1/2}$?

$C = -(0.5 \text{ mg/ml/hr})(72 \text{ hr}) + 125 \text{ mg/ml}$

C= 89 mg/ml remaining after 3 days

$t_{1/2} = 0.5 (125 \text{ mg/ml})/(0.5 \text{ mg/ml/hr})$

$t_{1/2} = 125$ hours

Example : How long will it take for this suspension to reach 90% of its original concentration?

90% x 125 mg/ml = 112.5 mg/ml

$$t = \frac{C - C_0}{-k_0} = \frac{112.5 - 125}{-0.5} = 25\ hr$$

First order

The **loss of drug is directly proportional to the concentration** remaining with respect to time and has the units of reciprocal time, that is, time^{-1}.

$$\ln C = -kt + \ln C_0$$

$$t_{1/2} = 0.693/k$$

Example: An ophthalmic solution of 5 mg/ml exhibits first-order degradation with a rate of 0.0005/day. How much drug will remain after 120 days, and what is its half-life?

$\ln C = - (0.0005/\text{day})(120\ \text{day}) + \ln(5\text{mg/ml})$

$\ln C = - 0.06 + 1.609 = 1.549$

$C = 4.71\ \text{mg/ml}$

$t_{1/2} = 0.693/0.0005/\text{day} = 1386\ \text{days}$

Example: how long will it take for the drug in the above ophthalmic solution to degrade to 90% of its original concentration?

90% of 5 mg/ml = 4.5 mg/ml

$\ln 4.5 = -(0.0005)\, t + \ln(5)$

$t = \ln 4.5 - \ln 5 \,/ -0.0005$

t = 210 days

containers, closures, other packaging features must be considered in stability testing:

- tablets or capsules packaged in **glass or plastic bottles** require different stability test from **blister or strip** packaging.

Drug instability detected by;

1. **change in physical appearance,**
2. **color,**
3. **odor,**
4. **taste of formula.**

- kinetic study begins by measuring **conc of drug** at given intervals under a specific set of conditions including **temp, pH, ionic strength, light,** and **drug conc**.
- **Measure drug's conc** at **various times** reveals stability or instability of drug.
- For example: the pH of solution may change while temperature, light intensity, and drug conc are held constant. The findings may be presented graphically, by **plot drug conc with time**. From the experimental data, the reaction rate may be determined and a **rate constant and half-life calculated.**

- **exaggerated temp, humidity, light**, to test stability of drug termed **accelerated stability**.
- Accelerated temp stability studies, for example: **6 months** at **40°C with 75%** humidity.
- If a significant change occurs lesser temp and humidity used, such as **30°C and 60%** relative humidity.
- Short-term accelerated studies used to determine the most stable formula for drug product.
- In stress testing, temp elevations in **10°C increments** higher than used in accelerated studies are employed until chemical or physical degradation.

- long-term (**12 months**) testing conducted **at 25°C and humidity 60%.**
- signs of degradation must be observed and reported:
- **Tablets:**

1. Appearance : Cracking, Chipping, Mottling.
2. friability,
3. Hardness.
4. Color.
5. Odor.
6. moisture content.
7. clumping, .
8. Disintegration.
9. dissolution.

- **Capsules:**

1. Moisture tackiness.
2. Color.
3. Appearance.
4. Shape.
5. Brittleness.
6. dissolution.

- **Oral solutions and suspensions:**

1. Appearance.
2. Precipitation.
3. pH.
4. Color.
5. Odor.
6. redispersibility (suspensions).
7. clarity (solutions).

- **Oral powders:** Appearance, color, odor, and moisture.

- **Metered-dose inhalation aerosols:**

1. Delivered dose per actuation.
2. number of metered doses.
3. Color.
4. particle size distribution,
5. loss of propellant.
6. pressure, valve corrosion.
7. spray pattern.
8. absence of pathogenic microorganisms.

- **Topical non metered aerosols:**

1. Appearance,
2. odor,
3. pressure,
4. weight loss,
5. net weight dispensed,
6. delivery rate.
7. spray pattern.

- **Topical creams, ointments, lotions, solutions, and gels:**

1. **Appearance,**
2. **color,**
3. **homogeneity,**
4. **odor,**
5. **pH,**
6. **resuspendability** (lotions),
7. **consistency,**
8. **particle-size distribution,**
9. **strength, and weight loss.**

Ophthalmic and nasal and oral inhalation:

1. Appearance.
2. Color.
3. Consistency.
4. pH,
5. clarity (solutions).
6. particle size and resuspendability (suspensions, ointments).
7. Strength.
8. sterility.

- **Small-volume parenterals**: Appearance, color, particulate matter, dispersibility (suspensions), pH, sterility, pyrogenicity, and closure integrity.
- **Large-volume parenterals**: Appearance, color, clarity, particulate matter, pH, volume sterility, pyrogenicity, and closure integrity.

- **Suppositories:**

1. Softening range,
2. Appearance.
3. melting.

- **Emulsions:**

1. Appearance (separation),
2. color,
3. odor,
4. pH, and viscosity.

- **Controlled-release membrane drug delivery systems**: Seal strength of drug reservoir, decomposition products, membrane integrity, drug strength, and drug release rate.

- Most products must have a **shelf life** of **2 or more years**.
- **Expiration date limits time** during which the product dispensed by pharmacist .

- **Prescriptions mixed by pharmacist do not require extended shelf life** because used immediately by patient and used only during immediate course of treatment.

- **nonaqueous liquids and solid 6 months**,
- for **water-containing** formula prepared from solid :**14 days**
- storage at **cold temp**; **30 days**.
- If oral aqueous liquid made from a tablet or capsule, the pharmacist should make up only **14 days'** supply, and must be stored in **refrigerator.**
- .

Chapter 4 part 2

Preformulation studies

Physical Description

Solid drugs :pure chemical compounds of either crystalline or amorphous constitution.

The **purity of chemical substance** is essential for its identification and for evaluation of its chemical, physical, and biologic properties.

Chemical properties include **structure**, **form**, and **reactivity**.

Physical properties include: **physical description**, **particle size**, **crystalline structure**, **melting point**, and **solubility**.

Biologic properties relate to its **ability to get to a site of action** to give **biologic response**.

Liquid drugs

- Many liquids are **volatile** and must be **physically sealed from atmosphere** to prevent evaporation loss.

- **Amyl nitrite**, for example, is a clear yellowish liquid that is volatile even at low temperatures and highly flammable. It is kept in small sealed glass cylinders wrapped with gauze.
- When amyl nitrite is administered, the glass is broken between the fingertips, and the liquid wets the gauze covering, producing vapors that are inhaled by patient requiring vasodilation.

Other example

Propyl hexedrine is volatile liquid that must be contained in a closed system. This drug is used as a nasal inhalant for vasoconstrictor action.

A cylindrical roll of fibrous material is impregnated with

Propyl hexedrine, and the saturated cylinder is placed in a suitable, **plastic, sealed nasal inhaler**.

The inhaler maintains its effectiveness for only a **limited time** because of the volatility of the drug.

Another problem associated with **liquid drugs** is that those intended for oral administration **cannot generally be formulated into tablet** without chemical modification.

An exception to this is liquid drug **nitroglycerin**, which is formulated into **sublingual tablets** that **disintegrate within seconds** after placement under the tongue.

However, because the drug is volatile, it has a tendency to escape from the tablets during storage,

the tablets sould be **stored in a tightly sealed glass container**.

when a liquid drug is to be administered orally and a solid dosage form is desired, one of two approaches is used.

First, liquid sealed in soft gelatin capsule. Vitamins A, D, and E are liquids available in capsule form.

Second, liquid drug developed into solid ester or salt so will be suitable for tablets or capsules.

Example: **scopolamine hydrobromide** is a solid salt of liquid drug scopolamine and is easily pressed into tablets.

Another approach to formulate liquids into solids is by **mixing drug with a solid or melted semisolid material**, such as a high molecular weight PEG. The melted mixture is poured into hard gelatin capsules to harden, and the capsules are sealed.

liquid drugs, that **taken orally in large doses** or **applied topically**, their liquid nature may have some advantage in therapy.

For example, 15-mL doses of mineral oil may be administered conveniently as such.

However, for pharmacists **prefer solid** materials in formulation work because they can easily form them into tablets and capsules.

Formulation and stability difficulties arise **less frequently with solid dosage forms than with liquid** for this reason, many new drugs first reach the market as tablets or capsules.

Later, liquid form of same drug marketed. This procedure is doubly advantageous, because physicians and patients prefer small, tasteless, accurately dosed tablets or capsules.

It is estimated that tablets and capsules constitute 70% of dosage forms.

pharmacists, dispense tablets twice as capsules.

Microscopic Examination

Microscopic examination of raw is important step in preformulation. It gives an indication of **particle size** and **crystal structure**.

Photomicrographs of initial and subsequent batch can provide important information in case of problems in formulation processing attributable to **changes in particle or crystal characteristics of drug.**

During some processing procedures, the solid drug powders must **flow freely**. Spherical and oval powders flow more easily than needle-shaped powders and make processing easier.

Heat of Vaporization

- Heat of vaporization of liquid: is the **amount of heat absorbed when 1 g of liquid vaporizes** and measured in **calories**.
- The heat of vaporization of water at 100°C is 540 cal/g

- **use of vapor pressure is important in implantable pumps delivering medications and in aerosol dosage forms.**

- Some **volatile** drugs can **migrate within a tablet** dosage form so the distribution may not be uniform any longer. So drug in one portion may be higher or lower than in the other portion.

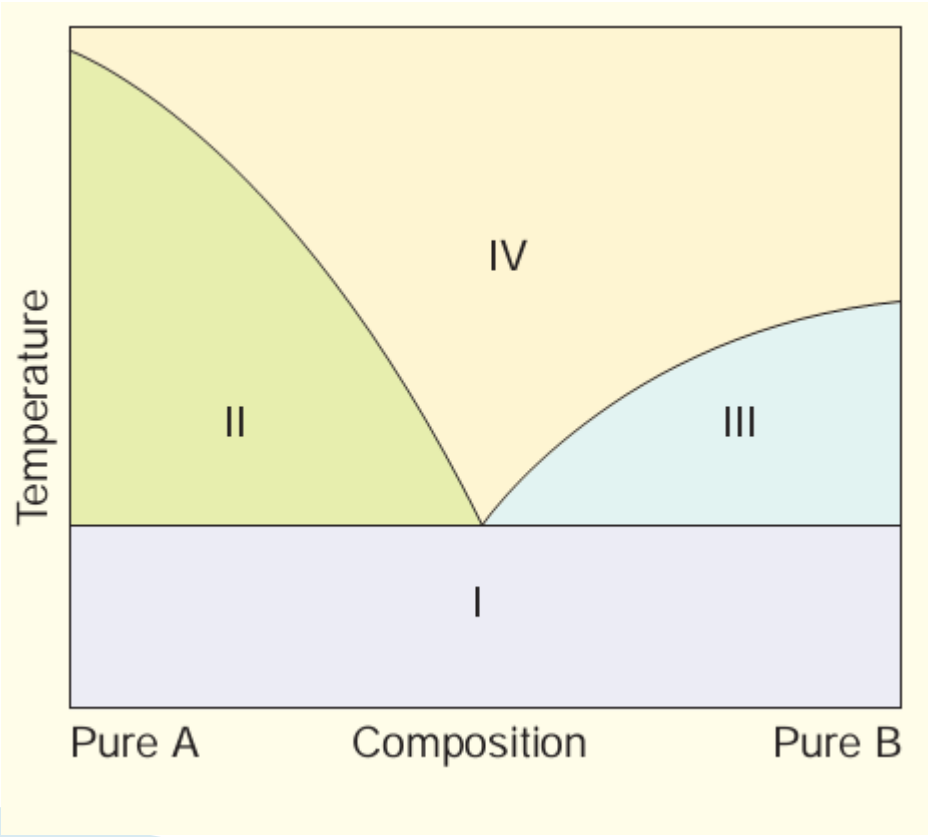
Melting Point Depression

- A characteristic of a pure substance is a defined melting point or melting range.
- If **not pure**, the substance will exhibit a **change in melting point**.
- This phenomenon is commonly used to determine the purity of a drug and compatibility of various substances before inclusion in the same dosage form.

The Phase Rule

Phase diagrams are used to **provide visual picture of the existence and extent of the presence of solid and liquid phases in binary, ternary**, and other **mixtures.**

I. Solid A + solid B
II. Solid A + melt
III. Solid B + melt
IV. Melt



The Phase Rule

A phase diagram, or temperature composition diagram, represents the melting point as a function of composition of two or three component systems.

The figure is an example of such a representation for a two-component mixture. This phase diagram depicts a two component mixture in which the components are completely miscible in the molten state and no solid solution or addition compound is formed in the solid state. As is evident, starting from the extremes of either pure component A or pure component B, as the second component is added, the melting point of the pure component decreases.

Particle Size

physical and chemical properties of drug are affected by particle size which are :**dissolution rate**, **bioavailability**, **content uniformity**, **taste**, **texture, color, stability**.

In addition**, flow ch**aracteristics and **sedimentation rates**, are important factors related to particle size.

particle size affect absorption profiles of certain drugs, including **griseofulvin, nitrofurantoin, spironolactone, and procaine penicillin.**

Also, satisfactory **content uniformity** in solid dosage forms depends on **particle size** and the equal distribution of the active ingredient through-out the formulation.

Polymorphism

- An important factor on formulation is crystal or amorphous form of drug.
- Polymorphic forms usually exhibit different physicochemical properties, including **melting point** and **solubility**.
- Polymorphic forms in drugs are relatively common. It has been estimated that at least **one third** of all organic compounds **exhibit polymorphism**

In addition to polymorphic forms, compounds may occur in non crystalline or amorphous forms. The energy required for a molecule of drug to escape from a crystal is much greater than is required to escape from an amorphous powder. Therefore, amorphous form is **always more soluble than crystal form**.

- The changes in crystal characteristics can influence **bioavailability** and **chemical and physical stability**. For example, it can be a significant factor relating to tablet formation because of flow and compaction behaviors.

Various techniques are used to determine crystal properties:

1. **hot stage microscopy**,
2. **thermal analysis**,
3. **infrared spectroscopy**, and
4. **x-ray diffraction**

Solubility

- important especially **aqueous solubility**. A drug must possess some aqueous solubility for therapeutic efficacy.

For a drug to **enter the systemic circulation** and exert a **therapeutic** effect, it must first be in solution.

- Relatively **insoluble compounds exhibit incomplete absorption**.

If the solubility of the drug substance is less than desirable, should improve solubility. The methods used depend on chemical nature of drug and type of drug product under consideration.

- Chemical modification of the drug into **salt or ester** forms is frequently used to increase solubility.

Equilibrium solubility method

A drug's solubility is usually determined by the equilibrium solubility method, by which an excess of the drug is placed in a solvent and shaken at a constant temperature over a long period until equilibrium is obtained. Then chemical analysis of the drug content in solution is performed to determine degree of solubility.

Solubility and Particle size

The **particle size** and **surface area** of a drug exposed to a medium can affect actual solubility within reason, for example, in the following relationship:

$$\log \frac{S}{S_0} = \frac{2\gamma V}{2.303\ RTr}$$

where

S is the solubility of the small particles,
S_0 is the solubility of the large particles,
γ is the surface tension,
V is the molar volume,
R is the gas constant,
T is the absolute temperature, and
r is the radius of the small particles.

The equation can be used to estimate the decrease in particle size required to increase solubility. For example, a desired increase in solubility of 5% would require an increase in the S/S_0 ratio to 1.05; that is, the left term in the equation would become log 1.05. If a powder has a surface tension of 125 dynes/cm, molar volume of 45 cm^3, and temperature of 27°C, what is the particle size required to obtain the 5% increase in solubility?

$$\log 1.05 = \frac{(2)(125)(45)}{(2.303)(8.314 \times 10^7)(300)r}$$

$$r = 9.238 \times 10^{-6} \text{ cm or } 0.0238\ \mu$$

A number of factors are involved in actual solubility enhancement, and this is only an introduction to the general effects of particle size reduction.

Solubility and pH

- To formulate liquid product, should adjust the pH of solvent to enhance solubility.

for many drug substances, pH adjustment is not an effective means of improving solubility.

- Weak acidic or basic drugs may require extremes in pH that are outside accepted physiologic limits or that may cause stability problems with formulation ingredients.

Adjustment of pH usually has little effect on the solubility of substances other than electrolytes. In many cases, it is desirable to improve aqueous solubility by:

1-use cosolvents

2-complexation,

3-micronization,

4-solid dispersion.

Dissolution

dissolution rate, or the time it takes for the drug to dissolve in the fluids at the absorption site, is the rate-limiting step in absorption.

This is true for drugs administered orally in **solid forms**, such as **tablets**, **capsules**, or **suspensions**,

and for those administered **intramuscularly**.

When the dissolution rate is the rate-limiting step, anything that affects it will also **affect absorption**. Consequently, **dissolution rate** can affect the **onset**, **intensity**, and **duration of response** and **control the overall bioavailability** of the drug from the dosage form

- The dissolution rate of drugs increased by:

1. decreasing drug's particle size.
2. Increase solubility in diffusion layer.
3. Use **highly water-soluble salt** of parent substance.

Dissolution rates of chemical compounds determined by two methods:

1. **The constant surface method**, which provides intrinsic dissolution rate of the agent.
2. **Particulate dissolution**, in which a weighed amount of the powdered agent is added to a fixed amount of solvent without exact control of surface area.

fick's laws of diffusion and Noyes-Whitney equation

- All drugs must diffuse through various barriers when administered to the body.

- Ficks low govern **absorption** through membrane
- Noyes-Whitney equation govern **dissolution** rate.

Membrane Permeability

- **passage of drug molecules across biologic membranes to produce a biologic response.**

- The biologic membrane acts as a **lipid barrier** to most drugs and permits the absorption of **lipid-soluble substances** by **passive diffusion**.
- while **lipid-insoluble** substances cannot diffuse across the barrier.

technique using **everted intestinal sac used to evaluate absorption of drug:**

In this method, a **piece of e intestine** is removed from intact animal, is **everted, and is filled with a solution** of drug, and the degree and rate of passage of the drug through the membrane sac are determined.

- In the latter stages of preformulation testing or early formulation studies, **animals and humans** must be studied to **assess absorption efficiency** and **pharmaco kinetic** parameters and to establish possible **in vitro and in vivo correlation** for dissolution and bioavailability.

Partition coefficient

$$P = \frac{(\text{Concentration of drug in octanol})}{(\text{Concentration of drug in water})}$$

P depends on drug concentration only if drug molecules have a tendency to associate in solution.

The oil–water partition coefficient is a measure of a molecule's **lipophilic character**; that is, its preference for the hydrophilic or lipophilic phase.

- If a solute is added to a mixture of two immiscible liquids, it will distribute between the two phases and reach an equilibrium at a constant temperature.

pKa /Dissociation constant

The extent of dissociation or ionization is highly dependent on **pH of medium** containing drug.

- In formulation, the vehicle is adjusted to a certain pH to obtain a certain level of ionization of drug for solubility and stability.
- In pharmacokinetic area, the extent of ionization of a drug has a strong effect on its extent of absorption, distribution, and elimination.
- dissociation constant, or pKa , is usually determined by potentiometric titration.

Hydrates and Solvates

Many active pharmaceutical agents exist as hydrates or solvates; some are hygroscopic, deliquescent, and/or efflorescent.

Hygroscopic powders are those that will tend to **absorb moisture** from the air.

Deliquescent powders are those that will absorb moisture from the air and even liquefy.

Efflorescent powders are those that may give up their water of crystallization and may even become damp and pasty.

When working with these powders, extra care must be taken.

if a hygroscopic or deliquescent powder is being weighed on a balance, the powder may absorb moisture from air and weigh heavier than it should. Therefore, weighings should be made quickly after opening the bulk chemical containers and then resealing them.

Solvates and hydrates must be packaged in "tight" containers to prevent the loss or gain of moisture.

In fact, it is best to have **all chemicals stored** in "tight" containers and to keep them closed at all times except for the short time when a weighing step is involved. Storage at the indicated temperatures is also important and to minimize any exposure to very high humidity levels.

organic Salt considerations

Because many drugs are either weak acids or weak bases and have limited water solubility, they are often used as their "salts" to increase their aqueous solubility.

For example: sodium salicylate is salt of weak acid, salicylic acid, and sodium hydroxide).

Also, ephedrine hydrochloride can be prepared between a weak base, ephedrine, and hydrochloric acid.

Generally, the "**unionized" portion of drug in solution that will be absorbed for systemic effect**.

This is described by the "dissociation constant" or "pKa " of the drug.

Active pharmaceutical ingredient (API) in a salt form is not 100% active drug, it is important to know whether or not the dose of drug is based upon drug salt or drug base form.

The purpose of “salt” form is usually **to enhance solubility** of drug; but it may also **enhance stability** and change other attributes of the drug that **make it easier to handle** and manipulate for producing dosage forms.

the “unionized” portion of drug will exert effect in body

Potency–Designated active Pharmaceutical ingredients

API, is not 100% active drug in all cases. It is important to know the assayed potency designation of the ingredient so that appropriate allowances can be made to obtain the correct amount. This may be on the label or on the Certificate of Analysis.

Some APIs, including some antibiotics, endocrine products, biotechnology-derived products, biologics, etc., have potencies that are based on "activity" and are expressed in terms of "**units** of activity," "**micrograms per milligram**," or other standard terms of measurements. These are described for each API in USP.

- For example:

One unit of penicillin represents the specific activity in 0.6 mcg of sodium penicillin. Thus 1 mg of penicillin sodium represents 1667 units of penicillin.

EXAMPLE

A formula calls for 500 mg of neomycin sulfate. The label on the API shows 650 µg of neomycin activity per mg of powder. How much of this powder is required to provide the 500 mg of neomycin sulfate?

$$\frac{650\,\mu g}{1000\,\mu g} = \frac{500\,mg}{X}$$

X = 769 mg of the powder is required to provide 500 mg of actual neomycin sulfate.

Drug and drug Product stability

Stability studies conducted in preformulation phase include:

1- **solid-state stability of drug alone**

2- **solution-phase stability**

3-stability in presence of excipients.

Initial investigation begins with knowledge of the drug's **chemical structure**, which allows the preformulation scientist to anticipate possible degradation reactions.

Drug Stability: Mechanisms of Degradation

- Chemical : Chemically, drug substances are alcohols, phenols, aldehydes, ketones, esters, ethers, acids, salts, alkaloids, glycosides, and others, each with **reactive chemical groups** having different susceptibilities to chemical instability.

- Chemically, the most frequently encountered destructive processes are **hydrolysis** and **oxidation**.

- **Hydrolysis** is a **solvolysis** process in which (**drug) interact with water** to yield **breakdown products**.

- For example, aspirin, or acetylsalicylic acid, combines with a water molecule and hydrolyzes into one molecule of salicylic acid and one molecule of acetic acid.

- Hydrolysis is probably the most important single cause of drug decomposition, mainly because a **great number of medicinal agents are esters** or contain such other groupings as substituted **amides**, **lactones**, and **lactams**, which are susceptible to the hydrolytic process.

- Another destructive process is **oxidation**, which destroys many drug, including: **aldehydes, alcohols, phenols, sugars, alkaloids, and unsaturated fats and oils.**

- **Chemically**, oxidation is loss of electrons from atom or molecule. Each electron lost is accepted by some other atom or molecule, reducing the recipient.
- In inorganic chemistry, oxidation is accompanied by increase in positive valence of an element: for example, ferrous (+ 2) oxidizing to ferric (+ 3).

- In organic chemistry, oxidation is frequently considered synonymous with **loss of hydrogen dehydrogenation**) from molecule.

Drug and Drug Product Stability: Kinetics and Shelf life

Stability is the extent to which a product retains within specified limits and through out its period of storage and use (i.e., its **shelf life**) the same properties and characteristics that it possessed at the time of its manufacture.

Five types of stability concern pharmacists:

1. Chemical: Each active ingredient retains its chemical integrity and labeled potency within the specified limits.
2. Physical: The original physical properties, including appearance, palatability, uniformity, dissolution, and suspendability, are retained.
3. Microbiologic: Sterility or resistance to microbial growth is retained according to the specified requirements. Antimicrobial agents retain effectiveness within specified limits.
4. Therapeutic: The therapeutic effect remains unchanged.
5. Toxicologic: No significant increase in toxicity occurs.

- Chemical stability is important for **selecting storage conditions** (temperature, light, humidity), selecting the proper container for dispensing (glass versus plastic, clear versus amber or opaque, cap liners), and anticipating interactions when mixing drugs and dosage forms.

- Stability and expiration dating are based on reaction kinetics, that is, the study of the rate of chemical change and the way this rate is influenced by concentration of reactants, products, and other chemical species and by factors such as solvent, pressure, and temperature.

Zero-order rate reactions

- If the loss of drug is independent on concentration of reactants and constant with respect to time (i.e., 1 mg/mL/h), the rate is called zero order. The mathematical expression is

$$\frac{-dC}{dt} = k_0$$

where k_0 is the zero-order rate constant [concentration (C)/time (t)].

The integrated and more useful form of the equation:

$$C = -k_0 t + C_0$$

where C_0 is the initial concentration of the drug.

- **<u>units for zero rate constant</u>** K_0 are concentration per unit time such as:
- **Mole/liter/ second** or **mg/ml/min**

- It is meaningless to attempt to describe the time required for all material in a reaction to decompose that is infinity therefore reaction rate are commonly described by K or by their half life $t_{1/2}$
- The half life equation for a zero order reaction
- $\mathbf{t_{1/2} = \frac{1}{2} (C_0/K_0)}$

Example1

- A drug suspension (125 mg/mL) decays by zero-order kinetics with a reaction rate constant of 0.5 mg/mL/h. What is the concentration of intact drug remaining after 3 days (72 hours), and what is its $t_{1/2}$?

$$C = -(0.5\,mg/mL/h)(72\,h) + 125\,mg/mL$$
$$C = 89\,mg/mL \text{ after } 3\,d$$
$$t_{1/2} = 1/2(125\,mg/mL)/(0.5\,mg/mL/h)$$
$$t_{1/2} = 125\,h$$

EXAMPLE 2

How long will it take for the suspension to reach 90% of its original concentration?

$$90\% \times 125\ \text{mg/mL} = 112.5\ \text{mg/mL}$$

$$t = \frac{C - C_0}{-k_0} = \frac{112.5\ \text{mg/mL} - 125\ \text{mg/mL}}{-0.5\ \text{mg/mL/h}} = 25\ \text{h}$$

Drug suspensions are examples of pharmaceuticals that ordinarily follow zero-order kinetics for degradation.

First order reactions

- If loss of drug is **directly proportional to concentration** remaining with respect to time, it is called a first-order reaction and has the units of **reciprocal time**, that is, time^{-1} The mathematical expression is:

$$\frac{-dC}{dt} = kC$$

where

C is the concentration of intact drug remaining,
t is time,
(dC/dt) is the rate at which the intact drug degrades, and
k is the specific reaction rate constant.

The integrated and more useful form of the equation:

$$\log C = \frac{-kt}{2.303} + \log C_0$$

where C_0 is the initial concentration of the drug.
In natural log form, the equation is

$$\ln C = -kt + \ln C_0$$

The units of k for a first-order reaction are per unit of time, such as per second.
The half-life equation for a first-order reaction is

$$t_{1/2} = 0.693 / k$$

- $T_{1/2}$ can be easily derived from first-order equation by substituting values of C = 50% and C0 = 100%, representing a decrease in concentration by 50%.

- Example 3

An ophthalmic solution of a mydriatic drug at 5 mg/mL exhibits first-order degradation with a rate of 0.0005/day. How much drug will remain after 120 days, and what is its half-life?

$$\ln C = -(0.0005/\text{d})(120) + \ln(5\ \text{mg/mL})$$
$$\ln C = -0.06 + 1.609$$
$$\ln C = 1.549$$
$$C = 4.71\ \text{mg/mL}$$
$$t_{1/2} = 0.693 / 0.0005/\text{d}$$
$$t_{1/2} = 1,386\ \text{d}$$

- Example 4

In Example 3, how long will it take for drug to degrade to 90% of its original concentration?

$$90\%\ \text{of}\ 5\ \text{mg/mL} = 4.5\ \text{mg/mL}$$
$$\ln 4.5\ \text{mg/mL} = -(0.0005/\text{d})t + \ln(5\ \text{mg/mL})$$
$$t = \frac{\ln 4.5\ \text{mg/mL} - \ln 5\ \text{mg/mL}}{-0.0005/\text{d}}$$
$$t = 210\ \text{d}$$

There are several **approaches** to **stabilize pharmaceutical** preparations containing drugs subject to **hydrolysis**:

1- Reduction or elimination of water from pharmaceutical system.

2- solid dosage forms containing water-labile drugs must be protected from humidity by applying a waterproof protective coating over tablets or by keeping the drug in a tightly closed container. It is fairly common to detect hydrolyzed aspirin by noticing odor of acetic acid upon opening a bottle of aspirin tablets.

3-In liquid preparations, water can be replaced by glycerin, propylene glycol, and alcohol. In certain injectable products, anhydrous vegetable oils may be used as the drug's solvent to reduce the chance of hydrolytic decomposition.

4- hydrolysis prevented in liquid drugs by suspending them in nonaqueous vehicle rather than dissolving them in aqueous solvent.

5-unstable antibiotic drugs, when an aqueous preparation is desired, the drug may be supplied to the pharmacist in a dry form for reconstitution by adding a specified volume of purified water just before dispensing.

6-Refrigeration is advisable for most preparations considered subject to hydrolysis.

7-Together with temperature, pH is a major determinant of the stability of a drug prone to hydrolytic decomposition. Hydrolysis of most drugs depends on relative concentrations of hydroxyl and hydronium ions, and a pH at which each drug is optimally stable can be easily determined. For most hydrolyzable drugs, optimum stability is on the acid side, somewhere between pH 5 and 6. Therefore, use of buffering agents, the stability of otherwise unstable compounds can be increased.

Buffers are used to maintain a certain pH

Buffer Capacity

pH, buffers, and buffer capacity are especially important in drug product formulation, since they affect the drug's solubility, activity, absorption, and stability and the patient's comfort.

A buffer is a system, usually an aqueous solution, that can resist changes in pH upon addition of acid or a base. Buffers are composed of a weak acid and its conjugate base or a weak base and its conjugate acid. Buffers are prepared by one of these processes:

1. Mixing a weak acid and its conjugate base or a weak base and its conjugate acid
2. Mixing a weak acid and a strong base to form the conjugate base or a weak base and a strong acid to form the conjugate acid

Using the Henderson-Hasselbalch equation:

Remember that acid is the proton donor and the base is the proton acceptor.

Example1

$$pH = pK_a + \log(base / acid)$$

EXAMPLE 1

A buffer is prepared by mixing 100 mL of 0.2 M phosphoric acid with 200 mL of 0.08 M sodium phosphate monobasic. What is the pH of this buffer? (K_a of phosphoric acid = 7.5×10^{-3})

Moles acid = (0.2 mol/1,000 mL) (100 mL) = 0.02 mol; (0.02 mol)/(0.3 L) = 0.067 M
Moles base = (0.08 mol/1,000 mL) (200 mL) = 0.016 mol; (0.016 mol)/(0.3 L) = 0.053 M
pKa = –log 7.5×10^{-3} = 2.125
pH = 2.125 + log (0.016 mol/0.02 mol) = 2.028

- Pharmaceutically, **oxidation** of a susceptible drug substance is most likely to occur when it is **not kept dry in the presence of oxygen** or when it is **exposed to light** or **combined with other chemical agents** without proper regard to their influence on oxidation.

- Oxidation of a chemical in a pharmaceutical preparation is usually accompanied by an **alteration in the color** of that preparation. It may also result in **precipitation** or a change in **odor**.
- Stability of the drug is preserved by agents called **antioxidants**

- Because oxygen may adversely affect their **stability**, certain pharmaceuticals require an **oxygen-free atmosphere** during preparation and storage.

- Oxygen may be present in pharmaceutical liquids in the airspace within the container or may be dissolved in the liquid vehicle.
- To avoid these exposures, oxygen-sensitive drugs may be prepared in the **dry state** and packaged in **sealed containers** with the **air replaced by an inert gas** such as nitrogen, as many liquid preparations. This is a common practice in commercial production of vials and ampules of easily oxidizable preparations intended for parenteral use.

- **Light** can also **act as a catalyst to oxidation** reactions, transferring its energy (photons) to drug molecules, making the latter more reactive through increased energy capability.

- As a precaution against acceleration of oxidation, sensitive preparations are packaged in **light-resistant** or opaque containers.

- Because most drug **degradations** proceed more rapidly as **temperature increases**, it is also advisable to maintain oxidizable drugs in a cool place.

- Another factor that can affect the stability of an oxidizable drug in solution is the **pH** of the preparation. Each drug must be maintained in solution at the pH most favorable to its stability. This varies from preparation to preparation and must be determined on an individual basis for each drug.

In summary, for easily oxidizable drugs, the formulation pharmacist may stabilize the preparation by the selective **exclusion from the system:** of **oxygen**, **oxidizing agents**, **trace metals**, **light**, **heat**, and other **chemical catalysts** to oxidation process.

Antioxidants, **chelating agents**, and **buffering agents** may be added to create and **maintain a favorable pH**.

In addition to oxidation and hydrolysis, destructive processes include:

- **polymerization**,
- **chemical decarboxylation**, and
- **deamination**. However, these processes occur less frequently and are peculiar to only small groups of chemical substances.

- **FDA-required demonstration of drug stability** is necessarily different for each stage of drug development, such as for a **2-week preclinical study**, an early **phase I study**, a **limited phase II trial**, **a pivotal phase III clinical study**, or for a new drug application.

- As a drug development program progresses, so do the requisite data to demonstrate and document the product's **stability profile**.

Before approval for marketing a product's stability must be assessed with regard to its formulation;

1. influence of its pharmaceutical ingredients;
2. influence of container and closure;
3. manufacturing and processing conditions (e.g., heat);
4. packaging components;
5. conditions of storage;
6. conditions of shipping,
7. temperature,
8. light, and
9. humidity; and
10. duration and conditions of pharmacy shelf life and patient use.
11. Holding intermediate product components (such as drug granulations for tablets) for long periods before processing into finished pharmaceutical products can affect the stability of

Both intermediate component and finished product.

Therefore, **in-process stability testing**, including **retesting of intermediate components**, is important.

Product containers, closures, and other packaging features must be considered in stability testing.

For instance, **tablets or capsules packaged in glass or plastic bottles** require **different stability test protocols from those for blister packs or strip packaging**.

Drugs particularly subject to **hydrolysis** or **oxidative** decomposition must be evaluated accordingly.

And sterile products must meet **sterility test** standards to ensure **protection against microbial contamination**. All **preservatives** must be tested for effectiveness in the finished product.

- **Study stability of drug products** by:

1. **long-term storage at room temperature and relative humidity**.
2. **accelerated stability studies** as indication of shelf life stability.

Drug instability in pharmaceutical formulations may be detected by change in physical appearance, color, odor, taste, or texture of formulation, whereas in other instances, chemical changes may not be self-evident and may be ascertained only through chemical analysis.

Scientific data pertaining to stability of formulation can lead to prediction of **expected shelf life** of proposed product, and when necessary to redesign of drug (e.g., into more stable salt or ester form) and to reformulation of the dosage form. Obviously, the rate at which a drug product degrades is important.

- **study of rate of chemical change** and the way it is influenced by such factors as:

1. **concentration of drug or reactant**,
2. the **solvent,**
3. **temperature and**
4. **pressure**, and
5. **other chemical agents** in the formulation .

- In general, a kinetic study begins by measuring:
- the concentration of drug at given intervals under a specific set of conditions, including **temperature, pH, ionic strength, light intensity, and drug concentration.**

The measurement of the drug's concentration at the various times reveals the stability or instability of the drug under the specified conditions with the passage of time.

From this starting point, each of the original conditions may be varied to determine the influence of such changes on drug's stability.

For example, the **pH of the solution may be changed** while the **temperature, light intensity, and original drug concentration** are held **constant**.

accelerated Stability Studies

- stability testing is to provide evidence on how the quality of a drug product varies with time under the influence of environmental factors, such as **temperature**, **humidity, oxidation, light and microbial exposure**. Stability testing is also used to establish the shelf life for a drug product and recommended storage conditions

Accelerated testing:

- Studies designed to increase the rate of chemical degradation or physical change of a drug substance or drug product by using exaggerated storage conditions as part of long-term, intermediate, and accelerated studies.

Expiration date: **The date placed on container label** of drug product designating the time prior to which a batch of the product is expected to remain within approved shelf life specification, if stored under defined conditions, and after which it must not be used.

Shelf life (also referred to as **expiration dating** period):The time period during which a drug product is expected to remain within the approved shelf life specification, provided that it is stored under the conditions defined on container label.

Stress testing (drug substance):

Studies undertaken to elucidate the **intrinsic stability of a drug** substance. Such testing is part of the drug development process and is normally carried out under more severe conditions than those used for accelerated testing.

Stress testing (drug product):**Studies undertaken to assess the effect of severe conditions on drug product**. Such studies include photostability testing as well as the specific testing of certain product types (e.g., metered dose inhalers, creams, emulsions).

For the drug substance, the testing should evaluate its **susceptibility to hydrolysis across a wide range of pH values** when **in solution or suspension**.

Photo stability testing should be an integral part of stress testing.

Data should be obtained from at least **three pilot-scale batches** of the drug substance, manufactured by the method and procedures that mirror the process to be used for final full-scale production batches.

Stability studies also should be **conducted on drug substance packaged in the container closure system** that is the same or simulates the packaging proposed for final product.

Table 4.2 EXAMPLE PROTOCOL FOR DRUG AND/OR DRUG PRODUCT STABILITY STUDIES[a]

STUDY TYPE	STORAGE CONDITION	MINIMUM TIME PERIOD
Long term	25°C ± 2°C @ 60% RH[b] ± 5% RH	12 mo
Intermediate	30°C ± 2°C @ 65% RH[a] ± 5% RH	6 mo
Accelerated	40°C ± 2°C @ 75% RH[a] ± 5% RH	6 mo

[a]For chemical entities. Adapted from Stability and Testing of New Drug Substances and Products. Available at: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm128204.pdf. (Accessed September 28, 2012).
[b]RH, relative humidity.

- on at least **three batches of manufactured dosage** form, packaged in the container and closure system, including all secondary packaging (e.g., outer carton) proposed for marketing.

- The testing should cover, as appropriate, the **physical, chemical, biological, and microbiological** attributes; **preservative content** (e.g., **antioxidant, anti-microbial preservative**); and functionality tests (e.g., metered-dose delivery system).

- Following FDA product approval and initial marketing, pharmaceutical manufacturers retain production samples of drug/drug product for **5 years or longer** and continue studies for signs of degradation under various conditions of storage.
- Pharmacy practitioners should also observe **signs of product instability** (e.g., color change, distorted capsules, softened tablets, etc.) and report such findings.

- Prescriptions requiring compounding by pharmacist do not require extended shelf life that commercially manufactured and distributed products do because they are intended to be **used immediately** by patient and used only during immediate course of prescribed treatment

USP guidelines on stability

state that in the absence of stability information applicable to a specific drug and preparation, the following guidelines can be used:

non aqueous liquids and solid formulations when manufactured drug is the source of the active ingredient, not later than 25% of the time remaining until the product's expiration date or 6 months; non aqueous liquids and solid formulations in which a USP or National Formulary (NF) substance is the source of active ingredient, a beyond-use date of 6 months;

for water-containing formulations prepared from ingredients in solid form, a beyond-use date not later than 14 days in storage at cold temperatures;

for all other formulations, a beyond-use date of intended duration of therapy or 30 days. Thus, if oral aqueous liquid preparation is made from a tablet or capsule formulation, the pharmacist should make up only at most 14 days' supply, and it must be stored in a refrigerator.

Furthermore, the pharmacist must dispense the medication in a **container conducive to stability** and use and must **advise the patient of proper method of use and conditions of storage** of the medication

Dosage Form Design

General outline of the course

- New drug development and approval process.
- Dosage form design: pharmaceutical and formulation consideration.
- Dosage form design: Biopharmaceutical and pharmacokinetic consideration.
- Current good manufacturing practices (cGMP).

New drug development and approval process

Objectives :

1. Difference between Investigational New Drug (IND) Application and a New Drug Application (NDA)
2. Differentiate between Phase 1, Phase 2, Phase 3, and Phase 4 clinical trials.
3. Give examples of the sources of new drugs
4. Differentiate between the various methods of drug discovery
5. Delineate the circumstances whereby an old drug could be classified as “new”
6. Define pharmacology, drug metabolism, and toxicology
7. Explain a treatment IND and an orphan drug
9. Define a package insert and the information contained therein

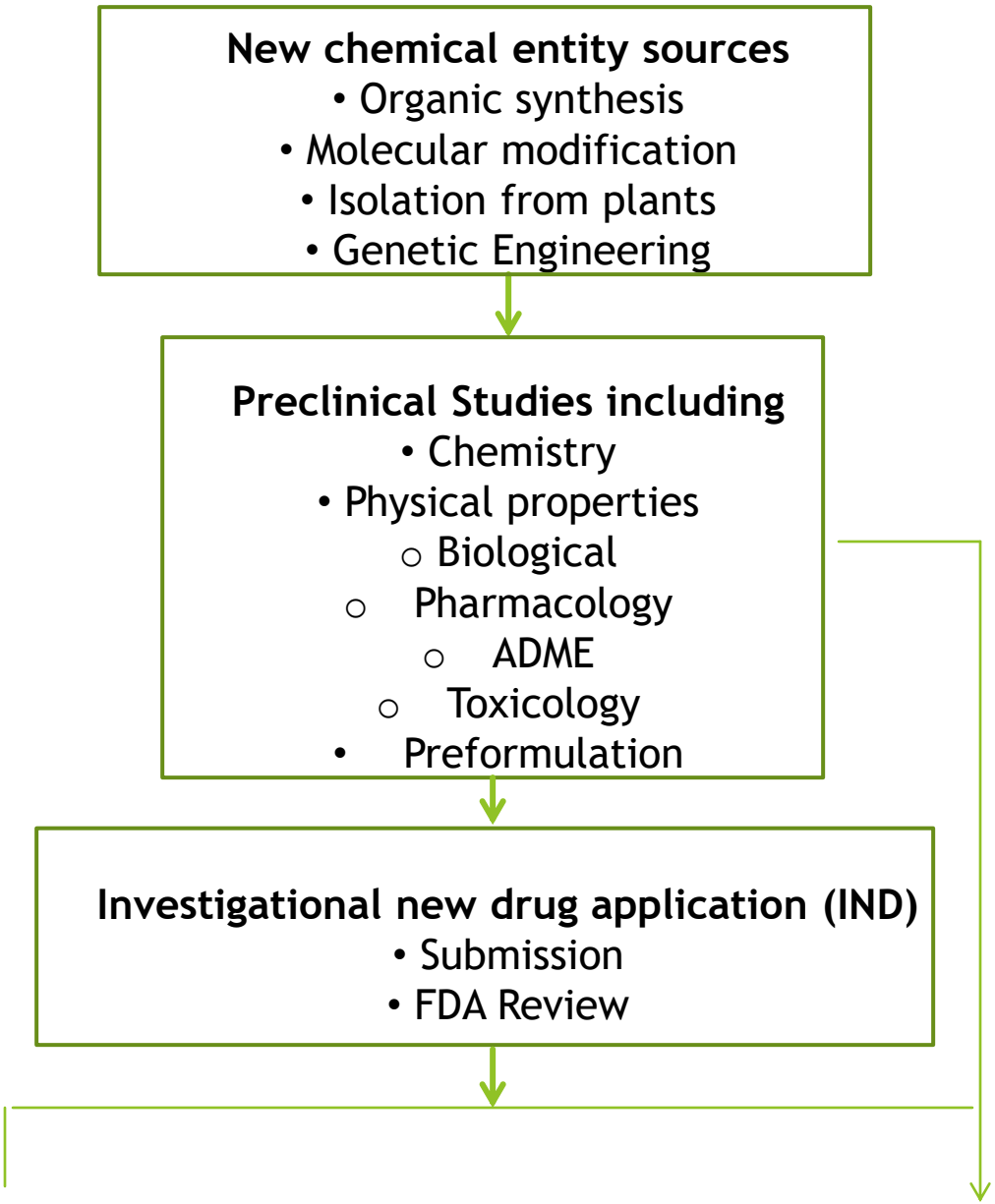
New Drug Development and Approval Process

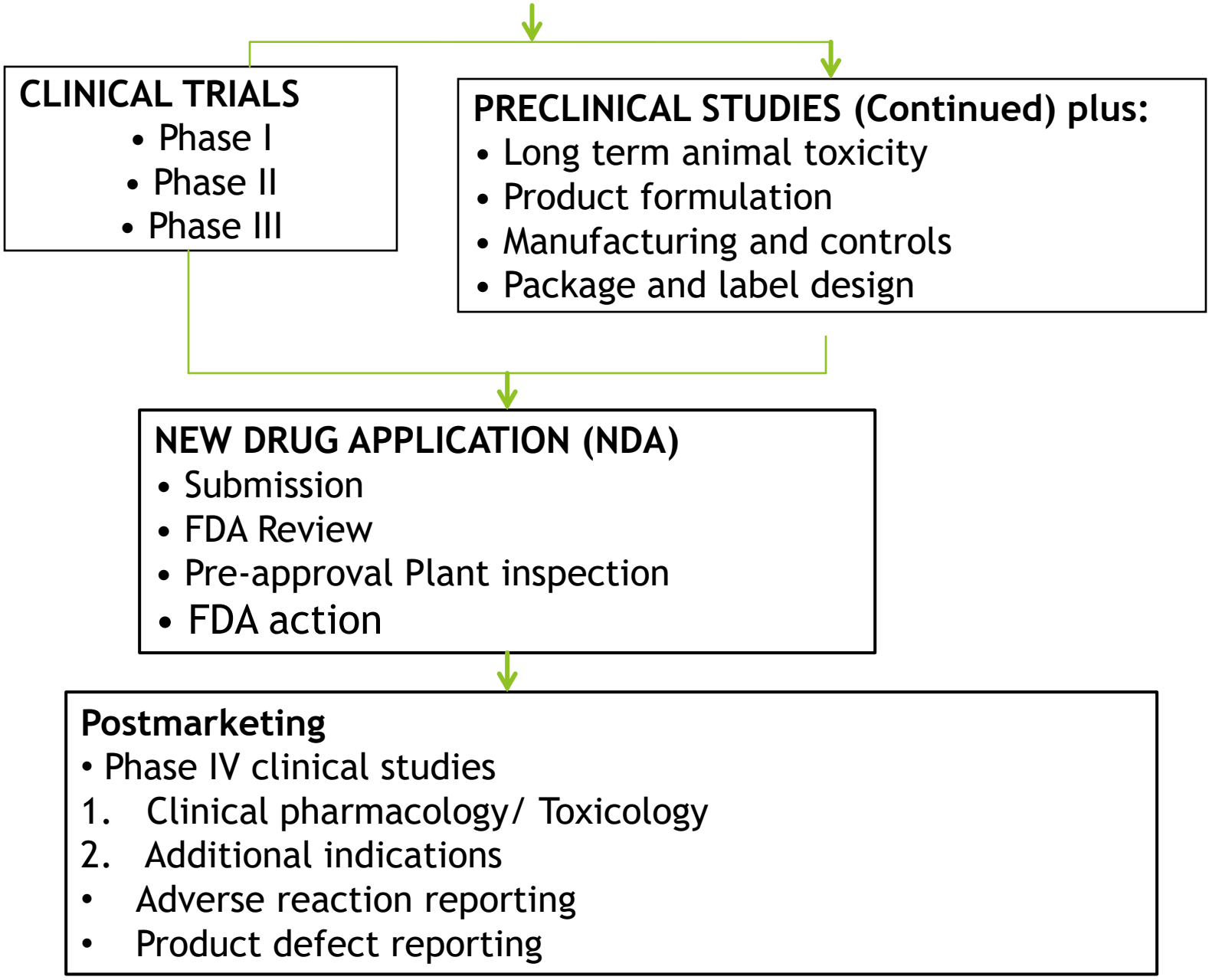
- To gain approval for marketing, a drug's sponsor (e.g., a pharmaceutical company) must demonstrate, through supporting scientific evidence, that

1. The new drug or drug product is safe and effective for its proposed use.
2. The various processes and controls used in producing the drug substance and in manufacturing, packaging, and labeling are properly **controlled and validated** to ensure that the product meets the established standards of quality.

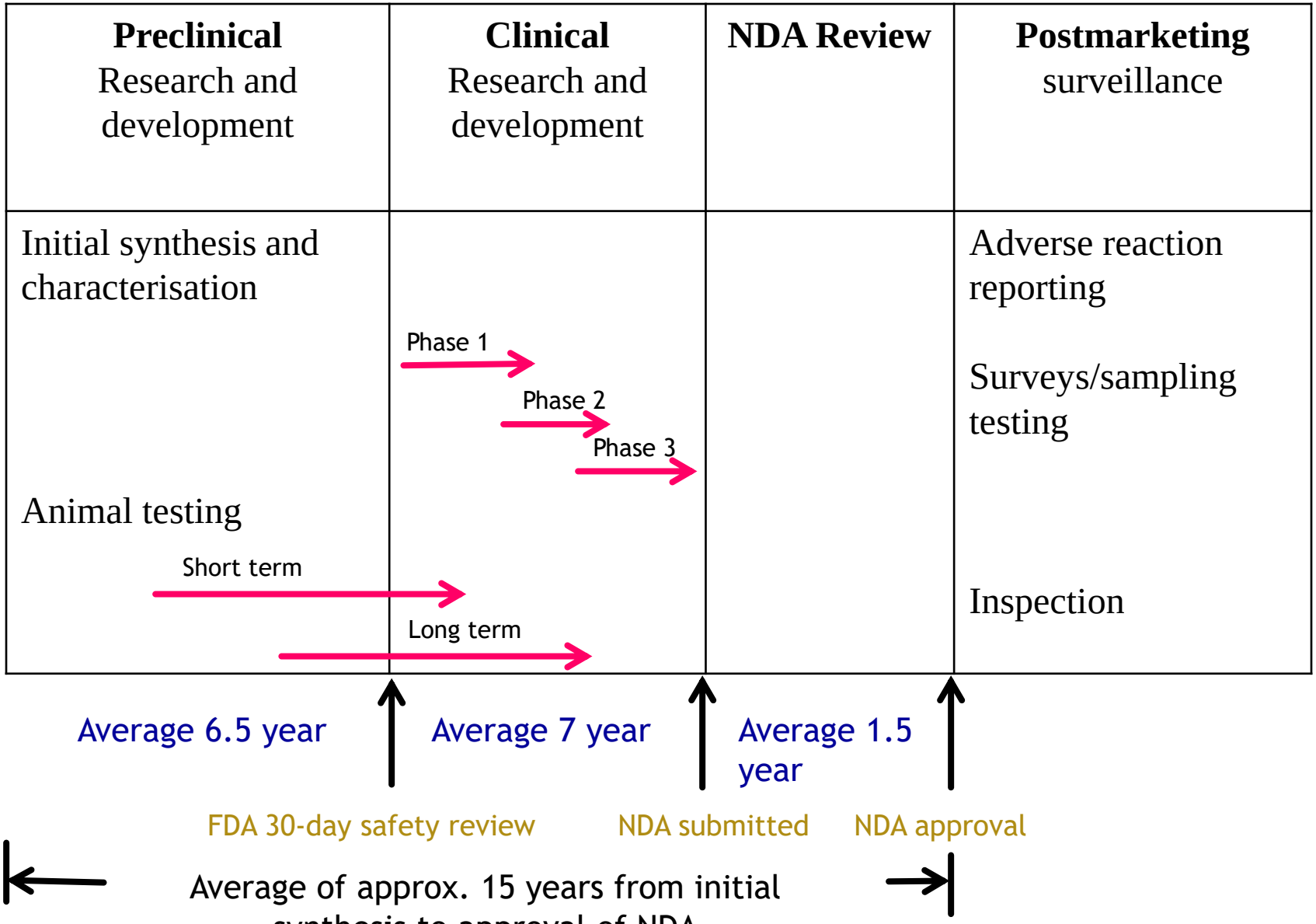
- The process and time course from drug discovery to approval for marketing can be lengthy and tedious

A schematic representation of the process for new drug development




CLINICAL TRIALS
• Phase I
• Phase II
• Phase III
PRECLINICAL STUDIES (Continued) plus:
• Long term animal toxicity
• Product formulation
• Manufacturing and controls
• Package and label design
NEW DRUG APPLICATION (NDA)
• Submission
• FDA Review
• Pre-approval Plant inspection
• FDA action
Postmarketing
• Phase IV clinical studies
1. Clinical pharmacology/ Toxicology
2. Additional indications
• Adverse reaction reporting
• Product defect reporting

Time course for the development of a new drug



- What does FDA approval indicate?

The FDA approval of a NDA indicates that the body of scientific evidence submitted sufficiently demonstrates:

- **that the drug or the drug product is safe and effective for the proposed clinical indication,**
- **that there is adequate assurance of its proper manufacture and control, and**
- **that the final labelling accurately presents the necessary information for its proper use.**

Some products, however, have been approved and later removed from the market for safety reasons, for example:

- alosetron HCL (Lotrovec), serious life-threatening gastrointestinal adverse effects, but was reintroduced in 2002 with availability and use restricted.

- astemizole (Hismanal), potentially fatal side effects (arrhythmias)

- cisapride (Propulsid), dexfenfluramine HCL (Redux), fenfluramine HCL (Pondimin).

- In addition to the general new drug approval process, special regulations apply for the approval of certain new drugs to treat serious or life-threatening illnesses, such as AIDS and cancer. **These may be placed on an accelerated or fast-track program for approval.**
- Treatment IND.

  If there is no satisfactory approved drug or treatment for a serious medical condition, a special protocol may be issued permitting the use of investigational drug to treat some patient prior to approval of the NDA.
- Treatment INDs often sought for orphan drugs, which are targeted for small numbers of patients who have rare conditions or diseases for which there are no satisfactory alternative treatments. Example, Penicillamine was developed to treat Wilson's disease, a rare hereditary disease

- For certain changes in a previously approved NDA, such as a labelling or a formulation change, a manufacturer is required to submit for approval a supplemental new drug application (SNDA).
- Abbreviated new drug application (ANDA)

  Is used to gain approval to market generic equivalent of a product that is already approved, in these instance the sponsor of the ANDA provides documentation on chemistry, manufacturing, controls (CMCs) and bioequivalence study.

- Medical devices such as catheters and pacemakers follows a separate approval process.

- Annually, approximately 40 new molecular entities receive FDA approval for marketing. In addition, many new dosage strength and dosage forms of previously approved drugs, new generic products, and new biologics are approved each year.

Source of new drugs

- **Natural sources :**

  e.g. plant extract from V. rosea yield two potent drugs that exhibited antitumor activities vincristine and vinblastine.

  Paclitaxel (Taxol) is another anticancer drug which is prepared from the extract of the Pacific yew tree.

- **Synthesized in the laboratory.**
- **Biotechnology.**
- **Animals:** drug testing, biologic assay, provided drugs that are from their tissues.

Examples of drugs from animal sources

- Hormonal substances (thyroid extract, insulin, pituitary hormone) obtained from the endocrine glands of cattle, sheep, and swine.

- The urine of pregnant mares is a rich source of estrogens.

- (serums, antitoxins, vaccines): poliomyelitis vaccine is prepared in cultures of renal monkey tissue, the mumps and influenza vaccines in fluid of chick embryo, the rubella (German measles) vaccine in duck embryo.

- New vaccines for diseases such as AIDS and cancer are being developed through the use of cell and tissue cultures.

- The two basic technologies that drive the genetic field of drug development are:

1. Recombinant DNA: genetic material can be transplanted from the higher species such as human into a lowly bacterium. It has the potential to produce almost any protein (e.g. human insulin, human growth hormone, hepatitis B vaccine, interferon)
2. Monoclonal antibody production. Conducted entirely in the cells of higher animals, including human. The technique exploits the ability of cells with the potential to produce a desired antibody and stimulates an unending stream of pure antibody production. These antibodies have the capacity to combat the specific target.

- Common to each technique is the ability to manipulate and produce proteins.

- Monoclonal antibodies application
  - Diagnostic medicine such as home pregnancy testing products. In these tests the mAb is highly sensetive to binding to human chorionic gonadotropins (HCG), a specific marker to pregnancy. Their use ensures that a women can perform the test easily in a short period with high reproducibility and in an inexpensive manner.
  - Treatment of diseases: Many FDA-approved mAb are now in current use such as: mumab (lupus erythematosus), Abciximab (antiplatelet), natalizumab (multiple sclerosis), ranibizumab (macular degeneration) and tocilizumab (rheumatoid arthritis).

Human Gene therapy

is a medicinal intervention based on the modification of the genetic material of living cells. Cells may be modified:

- Outside the body (ex vivo)
- Inside the body (in vivo) by gene therapy products given directly to the patient.

- gene therapy entails the transfer of new genetic material to the cells of a patient with a genetic disease.
- The first human gene therapy used was to treat adnosine deaminase (ADA) deficiency, a condition that results in abnormal functioning of immune system. Therapy consisted of the administration of genetically modified cells capable of correcting ADA.

Methods of Drug Discovery

1. **Random or untargeted screening:** involves the testing of large numbers of synthetic organic compounds or substances of natural origin for biologic activity

Random screens may be use initially:

- To detect an unknown activity of the test compound or substance or
- To identify the most promising compounds to be studied by more sophisticated nonrandom or targeted screens to determine a specific activity

- sometimes promising compounds may be overlooked if the screening models are not sensitive enough to reflect accurately the specific disease against which the agent or its metabolites may be useful.

- Bioassays are used to differentiate the effect and potency (strength of effect) of test agent from those of controls of known action and effect.

- Newer methods, such as high-throughput screening, are capable of examining 15,000 chemical compounds a week using 10 to 20 biologic assays.

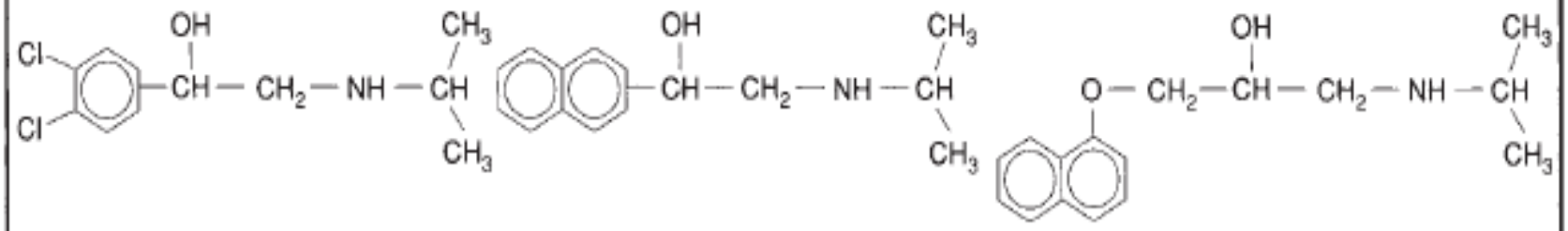
2. **Molecular modification:** is chemical alteration of a known and previously characterized organic compound (frequently a lead compound) for the purpose of enhancing its useful as a drug.

Purpose:

1. Enhancing its specificity for a particular body target site
2. Increasing its potency
3. Improving its rate and extent of absorption
4. Modifying to the advantage its time-course in the body
5. Reducing its toxicity
6. Changing its physical and chemical properties (e.g., solubility) to provide desired features.

The molecular modifications that led to the discoveries of the first commercial beta-blocker, propranolol (A), and the first commercial histamine H_2-receptor blocking agent, cimetidine (B).

A **BETA-BLOCKERS**

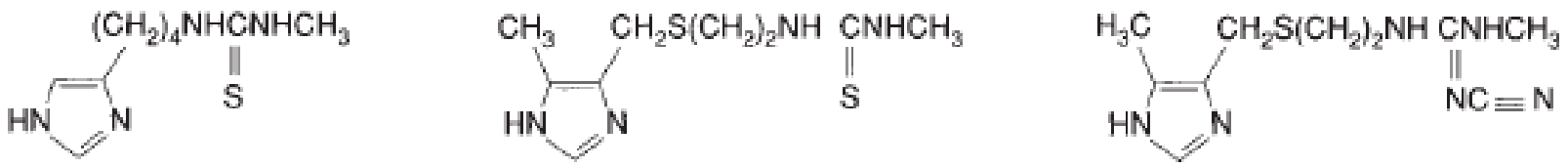


Dichloroisoproterenol 1957 → **Pronethalol** 1962 → **Propranolol*** 1964

Progress leading to the first commercial beta-blocker. Dichloroisoproterenol—first compound with beta-adrenoceptor blocking action; had partial agonist (sympathomimetic) activity. Pronethalol—beta-adrenoceptor blocking agent, relatively free from sympathomimetic activity. Clinical use limited by side effects, including light-headedness, incoordination, nausea and vomiting. Propranolol—beta-adrenoceptor blocking agent, free of sympathomimetic activity, and lacking side effects of pronethalol in humans.

B

H_2 ANTAGONISTS



Burimamide 1972 → **Metiamide** 1973 → **Cimetidine*** 1975

Progress leading to the first commercial ulcer drug. Burimamide—first histamine H_2-receptor blocking agent, poor oral availability. Metiamide—histamine H_2-receptor blocking agent, good oral bioavailability. Produced reversible agranulocytosis in some people. Cimetidine—histamine H_2-receptor blocking agent, good oral bioavailability. No agranulocytosis in man.

*Final Compound

3. Mechanism-based drug design: is a molecular modification to design a drug that interferes specifically with the known or suspected biochemical pathway or mechanism of a disease process

The intention is the interaction of the drug with specific cell receptors, enzymes systems, or metabolic process of pathogens or tumor cells, resulting in blocking, disruption, or reversal of the disease process.

- Molecular graphics: is the use of computer graphics to represent and manipulate the structure of a drug molecule to fit the simulated molecular structure of the receptor.

Example of Mechanism-based drug design
Enalaprilat (Vasotec), **Ranitidine (Zantac)** and **Sertraline (Zoloft)**

Lead compound: is a prototype chemical compound that has a **fundamental desired biologic** or **pharmacologic** activity and may lead to the development of a new drug.

- Although active, the lead compound may not possess all of the features desired, such as potency, absorbability, solubility, low toxicity, and so forth.

- The chemical modifications produce analogs with

1. additional or different functional groups.
2. Altered ring structures.
3. Different chemical configurations.

The results are modified chemical compounds capable of having different interactions with the body's receptors, thereby eliciting different actions and intensities of action.

- The synthesis of derivatives of the prototype chemical may ultimately lead to successive generations of new compounds of the same pharmacologic type.

Examples:

1. The development of new generations of cephalosporin antibiotics,
2. Additional H_2 antagonists from the pioneer drug Cimetidine.
3. The large series of antianxiety drugs derived from Benzodiazepine structure and the innovator drug chlordiazepoxide (Librium).

- Most drugs exhibit activities secondary to their primary pharmacologic action. Finasteride (Proscar) was originally approved to treat benign prostatic hyperplasia. Later, the same drug as (Propecia) was approved at lower recommended dosage to treat male pattern baldness.

Prodrugs: is a term used to described a compound that requires metabolic biotransformation following administration to produce the desired pharmacologically active compound.

Example of Prodrug: Enapril maleate (Vasotec)which, after oral administration, is bioactivated by hydrolysis to enaprilat, an ACE inhibitor used in the treatment of hypertension.

Prodrug may be design preferentially for

1. solubility, hydrocortisone sodium succinate
2. absorption,the addition of the decanoate ester to the haloperidol molecule makes the molecule less water soluble. Subsequently, when it is administered by a deep IM provides a sustained effect 4 W.
3. prolonged release
4. biostability

- If an active drug is prematurely destroyed by biochemical or enzymatic process, the design of a prodrug may protect the drug during its transport in the body.
  - valacyclovir is a prodrug of acyclovir. Normally, the bioavailability of acyclovir is 10% to 20% after oral administration. Valacyclovir is converted to acyclovir by liver esterases via the first pass metabolism resulting in a 55% bioavailability.

- In addition, the use of a prodrug could result in site-specific action of greater potency.
  - For example, dopamine in the treatment of parkinson disease is unable to cross the blood-brain barrier. However, its prodrug, levodopa, is able to cross the blood-brain barrier and then is converted to dopamine.

FDA's Definition of a New Drug

- **In general, a drug is considered a "new drug" (which will require a product specific application to be approved by FDA) if it is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the condition prescribed, recommended, or suggested in the labeling. This is irrespective of whether it is an OTC or a prescription drug.**

- **A new chemical entity (NCE) is, according to the U.S. Food and Drug administration, a drug that contains no active moiety that has been approved by the FDA in any other application.**

- **A new molecular entity (NME) is a drug that contains an active moiety that has never been approved by the FDA or marketed in the US.**

➢In addition, the following can be considered as a new drug:

1. A change in a previously approved drug product's formulation or method of manufacture constitutes a newness as such change may alter the safety and efficacy.

2. A combination of two or more old drugs or a change in the usual proportions of drugs in an established combination product if the change may alter safety or efficacy.

3. A proposed new use for an established drug, a new dosage schedule or regimen, a new route of administration, or new dosage form makes a drug or a drug product's status new and triggers reconsideration for safety and efficacy.

Drug Nomenclature

- When first synthesized or identified from a natural source, an organic compound is represented by an **empirical formula**, for example, $C_{16}H_{19}N_3O_5S.3H_2O$ for amoxicillin, which indicates the number and relationship of the atoms in the molecule.
- As knowledge of the relative locations of these atoms increases, the compound receives a **systematic chemical name**, such as

  6-[amino(4-hydroxyphenyl)acetyl]amino-3

- To be adequate and fully specific, name must reveal every part of the compound's molecular structure, so that it describes only that compound and no other.

- The systematic chemical name is generally so difficult that it soon is replaced in scientific communication by a shortened name, which, although less descriptive chemically, is understood to refer only to that chemical compound. This shortened name is **the chemical's nonproprietary (or generic) name** (e.g., amoxicillin).

- When the results of testing indicate that a compound shows sufficient promise of becoming a drug. The sponsor may formally propose a nonproprietary name to the U.S. Adopted Names (USAN) Council for **a proprietary or trademark name**.

- In contrast to the **proprietary or brand names or trademark names** given by the specific **manufacturers or distributors** of the drug, the term **generic name,** has been used extensively in referring to the **nonproprietary names** of the drugs.